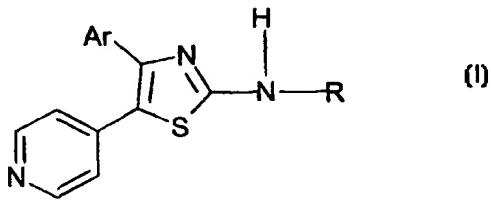




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| <p>(51) International Patent Classification ⁶ : C07D 417/04, 417/14, 213/50, A61K 31/44</p> | A1 | <p>(11) International Publication Number: WO 99/64418</p> <p>(43) International Publication Date: 16 December 1999 (16.12.99)</p> | | |
| <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(21) International Application Number: PCT/EP99/03859</p> <p>(22) International Filing Date: 3 June 1999 (03.06.99)</p> <p>(30) Priority Data: 9812117.1 5 June 1998 (05.06.98) GB 9818653.9 26 August 1998 (26.08.98) GB</p> <p>(71) Applicant (for all designated States except AT US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).</p> <p>(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HENG, Richard [FR/FR]; 58, rue de Mulhouse, F-68400 Riedisheim (FR). KELLER, Thomas, Hugo [CH/GB]; 27 Tanbridge Park, Horsham, West Sussex RH12 1SF (GB). PRESS, Neil, John [GB/GB]; 75 Manor Fields, Horsham, West Sussex RH13 6SD (GB).</p> <p>(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH).</p> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> </td> </tr> </table> | | | <p>(21) International Application Number: PCT/EP99/03859</p> <p>(22) International Filing Date: 3 June 1999 (03.06.99)</p> <p>(30) Priority Data: 9812117.1 5 June 1998 (05.06.98) GB 9818653.9 26 August 1998 (26.08.98) GB</p> <p>(71) Applicant (for all designated States except AT US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).</p> <p>(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HENG, Richard [FR/FR]; 58, rue de Mulhouse, F-68400 Riedisheim (FR). KELLER, Thomas, Hugo [CH/GB]; 27 Tanbridge Park, Horsham, West Sussex RH12 1SF (GB). PRESS, Neil, John [GB/GB]; 75 Manor Fields, Horsham, West Sussex RH13 6SD (GB).</p> <p>(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH).</p> | <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> |
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| <p>(54) Title: ARYL PYRIDINYL THIAZOLES</p> <div style="text-align: center; margin: 20px 0;">  </div> <p>(57) Abstract</p> <p>A compound which is of formula (I) or is a salt of a compound of formula (I), where Ar is an unsubstituted or substituted aryl group linked through an aromatic ring carbon atom thereof to the indicated thiazole ring and R is hydrogen, an acyl group or a monovalent aromatic group having up to 10 carbon atoms linked through an aromatic ring carbon atom to the indicated nitrogen atom, provided that R is not hydrogen when Ar is phenyl or 4-methoxyphenyl.</p> | | | | |

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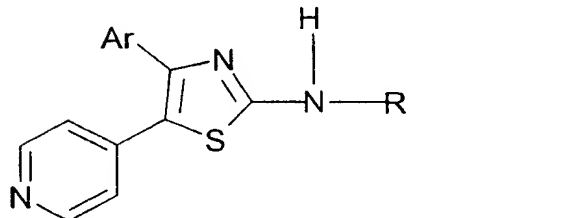
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ARYL PYRIDINYL THIAZOLES

This invention relates to aryl pyridinyl thiazoles, their preparation and their use as pharmaceuticals.

The invention provides, in one aspect, a compound which is of formula



or is a salt of a compound of formula I, where Ar is an unsubstituted or substituted aryl group linked through an aromatic ring carbon atom thereof to the indicated thiazole ring and R is hydrogen, an acyl group or a monovalent aromatic group having up to 10 carbon atoms linked through an aromatic ring carbon atom to the indicated nitrogen atom, provided that R is not hydrogen when Ar is phenyl or 4-methoxyphenyl.

Terms used in this specification have the following meanings:

“C₁ to C₈ alkyl” means alkyl having 1 to 8 carbon atoms and is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl or straight or branched octyl. Preferred is C₁ to C₄ alkyl.

“C₁ to C₈ alkoxy” means alkoxy having 1 to 8 carbon atoms and is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy or straight or branched pentoxy, hexyloxy or octyloxy. Preferred is C₁ to C₄ alkoxy.

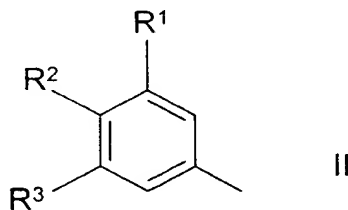
“C₅ to C₈ cycloalkyl” means cycloalkyl having 5 to 8 carbon atoms and is, for example, cyclopentyl, cyclohexyl, methylcyclohexyl, dimethylcyclohexyl, cycloheptyl and cyclooctyl. Preferred is C₆ to C₇ cycloalkyl.

“6-membered nitrogen heteroaryl group” means a 6-membered heteroaryl group having one, two or three nitrogen atoms such as pyridinyl (pyridyl), pyrimidinyl or triazinyl. Preferred is pyridinyl.

The group Ar in formula I may be an aryl group having up to 10 carbon atoms, e.g. phenyl or naphthyl, which may be unsubstituted or substituted, for example by one or more of the substituents hereinafter described. The total number of carbon atoms in Ar, including where present substituents attached to the aromatic ring, may be up to 50, for example up to 33 in preferred compounds and up to 13 in especially preferred compounds of formula III hereinafter described.

The group Ar is preferably phenyl which is unsubstituted or substituted by one or more substituents selected from halogen (more preferably chlorine or bromine), C₁ to C₈ alkyl (more preferably C₁ to C₄ alkyl), which is unsubstituted or substituted by halogen, which may be chlorine or, preferably, fluorine, C₁ to C₈ alkoxy (more preferably C₁ to C₄ alkoxy), C₇ to C₁₁ aralkyloxy (more preferably C₇ to C₉ aralkyloxy), in which the aryl moiety may be unsubstituted or substituted, for example by one or more halogen atoms, C₅ to C₈ cycloalkyl (more preferably C₆ to C₇ cycloalkyl), C₁ to C₈ alkylamino (more preferably C₁ to C₄ alkylamino) or di (C₁-C₈ alkyl)amino (more preferably di(C₁-C₄ alkyl)amino).

In some especially preferred embodiments, Ar is a group of formula

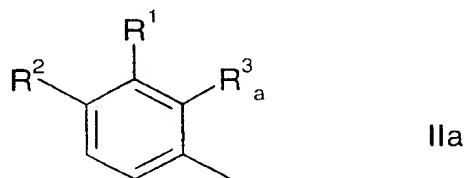


where R¹, R² and R³ are each independently hydrogen, halogen, unsubstituted or halogen-substituted C₁ to C₄ alkyl, C₁ to C₄ alkoxy, C₇ to C₉ aralkyloxy, C₆ to C₇ cycloalkyl, C₁ to C₄ alkylamino or di(C₁-C₄alkyl)amino.

In a group of formula II, in most of the preferred embodiments, one or two of R¹, R² and R³ are preferably hydrogen. Especially preferred groups of formula II are those in which R¹ is hydrogen, chlorine, bromine, methoxy or methyl, R² is hydrogen, chlorine, methyl, trifluoromethyl, isopropyl, n-butyl, cyclohexyl, methoxy, n-butoxy, benzyloxy or dimethylamino and R³ is hydrogen, methoxy or methyl.

In other especially preferred groups of formula II, R^1 is hydrogen or trifluoromethyl, R^2 is hydrogen, 3,4 dichlorobenzyloxy, 2-phenylethoxy, bromine, 4-methylbenzyloxy, or 4-chlorobenzyloxy, and R^3 is hydrogen.

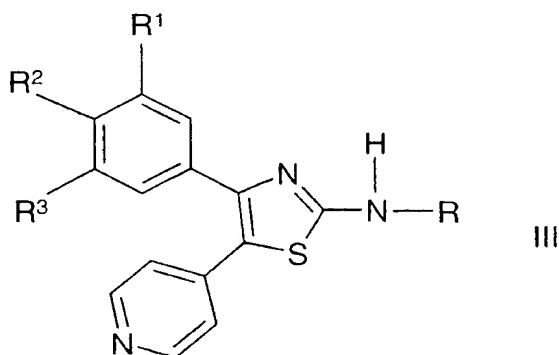
In another especially preferred embodiment, Ar is a group of formula



where R^1 and R^2 are as hereinbefore defined and R^3_a is C_1 to C_4 alkyl. An especially preferred group of formula IIa is that in which R^1 is hydrogen, R^2 is chlorine and R^3_a is methyl.

The group R in formula I is preferably hydrogen, an acyl group of formula R^4CO- where R^4 is a C_1 to C_4 alkyl group, or in alternative preferred embodiments R is phenyl which is unsubstituted or substituted, preferably by carboxy, or is a 6-membered nitrogen heteroaryl group. In a further preferred embodiment R is an acyl group of formula R^4_aCO- where R^4_a is a 5-membered heteroaryl group, preferably furyl. In some especially preferred embodiments, R is acetyl, isobutyryl, carboxyphenyl or pyridinyl. In other especially preferred embodiments R is propionyl or 3-furoyl.

Especially preferred compounds of the invention are those of formula I which are also of formula



and their pharmaceutically acceptable salts where R^1 , R^2 , R^3 and R are as hereinbefore defined, particularly where

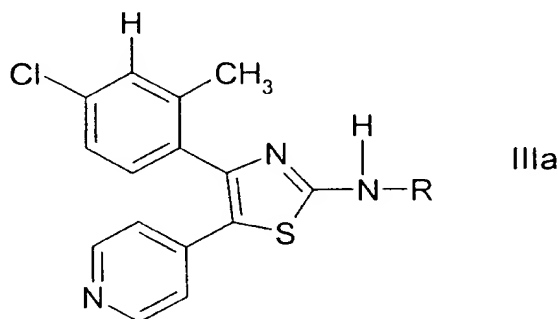
(i) R^1 and R^2 are chlorine, R^3 is hydrogen and R is hydrogen, acetyl, isobutyryl or 4-carboxyphenyl; or

- (ii) R^1 and R^3 are hydrogen, R^2 is methoxy or methyl and R is hydrogen, acetyl, pyridin-2-yl or pyridin-3-yl; or
- (iii) R^1 is bromine, R^2 is N-dimethylamino, R^3 is hydrogen and R is hydrogen or acetyl; or
- (iv) R^1 and R^3 are methyl, R^2 is hydrogen and R is hydrogen or acetyl; or
- (v) R^1 is methyl, R^2 is methyl, R^3 is hydrogen and R is hydrogen or acetyl; or
- (vi) R^1 and R^3 are hydrogen, R^2 is n-butoxy, benzyloxy, n-butyl, isopropyl, trifluoromethyl or cyclohexyl and R is hydrogen or acetyl; or
- (vii) R^1 , R^2 and R^3 are methoxy and R is hydrogen or acetyl.

Other especially preferred compounds are those of formula III and their pharmaceutically acceptable salts where

- (viii) R^1 is methyl, chlorine or trifluoromethyl, R^2 and R^3 are hydrogen and R is hydrogen or acetyl;
- (ix) R^1 is fluorine, R^2 is trifluoromethyl, R^3 is hydrogen and R is hydrogen or acetyl;
- (x) R^1 is hydrogen, R^2 is chlorine, R^3 is methyl and R is hydrogen or acetyl;
- (xi) R^1 and R^3 are hydrogen, R^2 is 3,4-dichlorobenzyloxy, 2-phenylethoxy, bromine, 4-methylbenzyloxy or 4-chlorobenzyloxy and R is hydrogen or acetyl;
- (xii) R^1 is methyl, chlorine or methoxy, R^2 is benzyloxy, R^3 is hydrogen and R is hydrogen or acetyl;
- (xiii) R^1 and R^3 are hydrogen, R^2 is benzyloxy, and R is 2-pyridinyl, 3-pyridinyl or 3-furoyl;
- (xiv) R^1 is methoxy, R^2 is benzyloxy, R^3 is hydrogen and R is propionyl; or
- (xv) R^1 , R^2 and R^3 are each hydrogen.

Further especially preferred compounds are those of formula

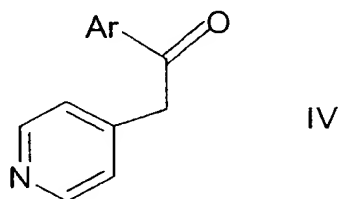


where R is hydrogen or acetyl, and pharmaceutically acceptable salts thereof.

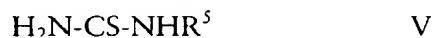
The compounds represented by the formulae (I) and (III) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propionic acid, butyric acid, hydroxy acids such as lactic acid, citric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

Compounds of formula (I) which contain acidic, e.g. carboxyl, groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures. These salts may be prepared from compounds of formula I by known salt-forming procedures.

Compounds of formula I may be prepared by reacting a compound of formula

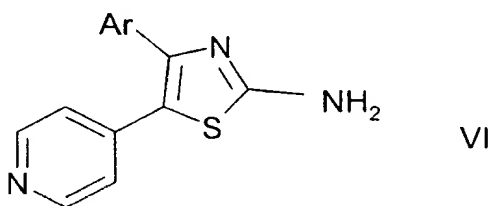


with halogen, preferably bromine, and then reacting the halogenated product with a compound of formula



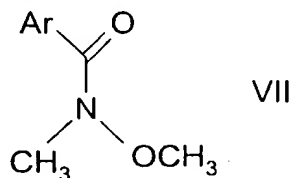
where Ar is as hereinbefore defined and R^5 is hydrogen, or a monovalent aromatic group having up to 10 carbon atoms linked through an aromatic ring carbon atom to the indicated nitrogen atom and, where R^5 is hydrogen and a compound of formula I in which R is acyl is desired, reacting the compound obtained with an acylating agent, for example an acid halide or anhydride of a carboxylic acid such as a carboxylic acid of formula R^4COOH where R^4 is C_1 to C_4 alkyl.

The reaction of the compound of formula IV with halogen may be carried out using known procedures for the halogenation of ketones, for example in an organic solvent such as dioxane and at a temperature of 10 to 40°C. The reaction of the halogenated intermediate with the compound of formula V may be carried out using known procedures for the reaction of alpha-halogenated carbonyl compounds with thioureas to form thiazoles, for example in an organic solvent such as ethanol and at reflux temperature; when R⁵ is hydrogen, this reaction results in the formation of a compound of formula I which is also a compound of formula



where Ar is as hereinbefore defined. This compound may be reacted with an acylating agent such as hereinbefore described, preferably acetyl chloride, propionyl chloride, isobutyryl chloride or 3-furoyl chloride, using known procedures for the acylation of amines, to give a compound of formula I where R is an acyl group.

Compounds of formula IV may be prepared by reacting a compound of formula



where Ar is as hereinbefore defined, with the reaction product of 4-picoline and an alkyl lithium such as butyllithium. Both reactions may be carried out at -30°C to 30°C in an organic solvent such as tetrahydrofuran.

Compounds of formula VII may be prepared by reacting a compound of formula

Ar-COOH, where Ar is as hereinbefore defined, with dimethylhydroxylamine hydrochloride using known procedures, for example in the presence of N,N¹-carbonylbisimidazole at reflux temperature in an organic solvent such as tetrahydrofuran.

Compounds of formula V are thioureas which are available commercially or may be obtained by known procedures. Compounds of formula IV are believed to be novel, with the exception of those where Ar is 4-methoxyphenyl, 4-methylphenyl, 3-bromo-4-

dimethylaminophenyl, 4-benzyloxyphenyl or 4-trifluoromethylphenyl. Compounds of formula VII are believed to be novel, with the exception of those where Ar is 4-methoxyphenyl, 4-methylphenyl, 3,4-dimethylphenyl, 3,4,5-trimethoxyphenyl, 3-bromo-4-dimethylaminophenyl or 4-trifluoromethylphenyl.

In another aspect, the invention relates to the use of compounds of formula I and their pharmaceutically acceptable salts, particularly as exemplified herein, as pharmaceuticals. In particular, the compounds of formula I and their salts, particularly where R is an acyl or monovalent aromatic group, and their salts, exhibit inhibition of human adenosine A3 receptor activation and, moreover, in general selectively inhibit activation of the human adenosine A3 receptor over the A1 receptor. Their inhibitory properties relative to the adenosine A3 and A1 receptors are demonstrated in the following test procedures:

Adenosine A3 receptor assay

The effect of compounds of the invention on the binding of [125 I]-AB-MECA (N6-4-amino-3-iodobenzyladenosine-5'-N-methyluronamide) to recombinant human adenosine A3 receptors is assessed in a 96 well plate-based filtration assay.

Chinese hamster ovary (CHO) cells lacking a functional gene for dihydrofolate reductase stably transfected (pXMT3 vector) with human A3 receptor cDNA are obtained from Research Biology Inc., Baltimore (RBI). The clone is specified by RBI to show >95% specific binding of [125 I]-AB MECA, 2000 fmol/mg maximal binding and a K_i value of 0.19nM.

The cells are cultivated according to the RBI protocol in sterile IMDM (Iscove's Modified Dulbecco's Medium, Seromed T046-10), supplemented with NaHCO_3 (24mg/l), Penicillin/Streptomycin solution (Seromed A2213) and 100ml/l fetal calf serum (Seromed S0115), at 37° C in an atmosphere of 5% CO_2 . For passaging, cells are trypsinised and split at dilutions below 1:50. Cells are grown to confluence in "Expanded Surface Area" tissue culture flasks (Cellon Sarl, Luxemborg, 4450-05), replacing the medium every 3 to 4 days.

Membranes are prepared according to the method published by Gallo-Rodriguez et al (J.Med. Chem 1994; 37 : 636-646), omitting incubation with adenosine deaminase.

The assay is carried out essentially as described by Gallo-Rodriguez et al in the abovementioned reference. 96-well glass filterplates (GF/B, Canberrra Packard) are soaked

with 50 µl/well ethyleneimine polymer (Fluka 5mg/ml water, soak time between 10 minutes and 2 hours) and washed 3 times with buffer just before use. Assays are carried out in flat- or round-bottomed 96-well microtitre plates in a total volume of 100 µl (25 µl of inhibitor solution containing 80 µl/ml of dimethyl sulfoxide (DMSO), 50 µl of membranes containing 10 to 25 µg of protein and 25 µl of [¹²⁵I]-AB-MECA (Amersham, 2000Ci/mmol, final concentration 12.5pM, 2.5 nCi/well). After 1 hour of shaking at room temperature, membranes are transferred onto the filterplates using a cell harvester (FilterMate) and washed 5 times.. Plates are dried either overnight or for at least 2 hours at 50° C. Each well receives 40 µl Microscint 40 (Canberra Packard) and is counted in a scintillation counter (TopCount, Canberra Packard). Nonspecific binding (blanks) is determined in the presence of 10 µM I-AB-MECA. Control wells receive 25 µl of 80µl/ml DMSO.

Inhibition is determined as $\frac{\text{sample} - \text{blank}}{\text{control} - \text{blank}} \cdot 100\%$.

Concentration-inhibition curves are constructed from a series of concentrations consisting of 7 distinct concentrations spanning at least 2 ; but usually 3 orders of magnitude. Curves are fitted to the data using the non-linear least squares fitting routines of Microcal Origin 4.1 (Slogistic 1) and results expressed as IC₅₀ (nM), the concentration of inhibitor at which 50% inhibition is obtained.

Adenosine A1 receptor inhibition assay

The effect of compounds of the invention on the binding of [³H]-DPCPX (8-cyclopentyl-1,3-dipropylxanthine) to recombinant rat adenosine A1 receptors transfected into Sf9 cells is assessed in a filtration assay.

Incubations are performed in plastic vials, in triplicate, in a final volume of 100 µl. For displacement binding, membranes (RBI, A-232) corresponding to 17 µg/tube are pre-treated with adenosine deaminase (3U/ml) and then incubated in Tris-HCl buffer (50mM, pH 7.4) containing MgCl₂ (10mM), EDTA (1mM), [³H]-DPCPX (0.32nM, SA = 4440 GBq/mmol) and the inhibitor of interest, for 1 hour at 4 °C. Membrane bound tracer is separated from free following dilution by 4ml wash buffer (Tris-HCl, 50mM, pH 7.4) followed by rapid filtration through Whatman GF/B glass fibre filters, which have been pre-soaked with polyethyleneimine (0.5% for 1h). This is followed by 3 x 3ml washings of the filters.

Radioactivity is measured in a scintillation counter. Specific binding of radioligand in the presence of inhibitor (calculated as total binding- non-specific binding) is normalised to the percentage of specific binding in the absence of inhibitor (max binding). IC_{50} values (nM) are derived by fitting the results obtained to the Hill equation.

The compounds of the Examples hereinbelow which are compounds of formula I where R is an acyl or monovalent aromatic group have IC_{50} values in the Adenosine A3 assay of the order of from 0.1 to 230 nM, mostly below 1nM, and have Selectivities (ratios of IC_{50} in adenosine A3 assay to IC_{50} in Adenosine A1 assay) of up to 10,000, mostly greater than 30. For example, the compounds of Examples 9, 10, 11 and 12 have IC_{50} values of 0.15nm, 0.23nm, 0.16nm and 0.39nm respectively, and Selectivities of 10,000, 6521, 118 and 3846 respectively

Compounds of formula I and their salts, particularly those where R is an acyl group, exhibit inhibition of adenosine A2b receptor activation. Their inhibitory properties relative to that receptor may be demonstrated in the following test procedure:

Adenosine A2b receptor assay

The procedure follows the protocol described by Martin, Eur.J.Pharmacol. 216, 235-242 (1992), with minor adaptations. Male albino guinea-pigs (300-400 g) are killed by a blow to the neck. Thoracic aortas are removed and put in a Krebs bicarbonate solution containing (nM): NaCl 122, KCl 5, $NaHCO_3$ 25, KH_2PO_4 1, $MgSO_4$ 1.2, $CaCl_2$ 1.25 and glucose 11.5. The vessels are cleared of adherent tissue under a microscope and cut into ring segments approximately 4 mm long. Rings are mounted in 20 ml organ baths containing the Krebs bicarbonate solution, gassed with 95% O_2 - 5% CO_2 at 37°C, under a tension of 2g. Isometric changes in tension are recorded. After a 1 hour period, during which the physiological solution is repeatedly renewed and the tension readjusted to 2 g, contraction is induced by repeated (3 times) addition of phenylephrine (3 μ M). After a stable contraction has been reached (60-90 minutes), 5¹-N-ethylcarboxamidoadenosine (NECA)(adenosine receptor agonist) is added cumulatively in the presence of phenylephrine. Each concentration (from 10⁻⁸M to 10⁻⁴M) is allowed to produce a stable effect before the next one is added. Following repeated washout (60-90 minutes), either the vehicle (aqueous 0.2% DMSO) or an antagonist under test in the vehicle is added 10 minutes prior to a further dose of phenylephrine and 30 minutes before starting the cumulative concentration-response curve to NECA. The antagonists have no agonist effects at the concentrations

used. Data are expressed in percent relaxation of the induced contraction. Concentration-response curves to NECA are monophasic up to a concentration of 10^{-4} M and are considered to reflect A_{2b} receptor activation. K_B values of antagonists are calculated from the shifts of NECA curve at the EC_{50} level of relaxation ($K_B = [\text{antagonist}] / (\text{concentration-ratio}-1)$). The vehicle used, aqueous 0.2% DMSO, has no effect per se.

Compounds of the Examples hereinbelow have K_B values of the order of from 2nM to 1 μ M. For example, the compounds of Examples 5, 35A and 36A have K_B values of 6nM, 5nM, and 2nM respectively.

Compounds for formula I where R is hydrogen, i.e. compounds of formula VI, and their salts, exhibit inhibition of tumour necrosis factor alpha (TNF- α) activation. Their inhibitory properties relative to TNF- α release may be demonstrated in the following test procedure:

TNF- α assay

Mononuclear cells (MNC) are isolated from blood of normal individuals by Ficoll-hypaque gradient centrifugation (20 min at 800xg). The interphase is collected, washed twice in phosphate buffered saline (PBS) and resuspended in RPMI1640 (GIBCO) supplemented with 10% fetal calf serum (FCS). Cell density is adjusted to 1×10^6 cell/ml. After 15 minutes preincubation together with the compound under test dissolved in dimethyl sulfoxide (DMSO), or in the absence of the compound in the control experiment, the cells are stimulated with lipopolysaccharide (LPS) (1 μ g/ml) and IFN- γ (10ng/mL) and supernatants are harvested after 24 hours of incubation at 37°C in a humidified incubator with 5% CO₂. Concentration of TNF- α in these supernatants is measured by sandwich ELISA using two monoclonal antibodies recognizing different epitopes of the specific cytokine (mAb357/101-4 and biotinylated 2-179/E11). Optical density is measured at 405 nm and cytokine concentration is calculated based on the results from serial dilutions of standard recombinant human TNF- α . Values for IC_{50} , the concentration of inhibitor at which 50% inhibition of TNF- α production is obtained, are obtained using the Origin programme. The compounds of formula VI in the Examples hereinbelow have IC_{50} values of the order of from 3 to 300nM.

The utility of compounds of the invention as anti-inflammatory agents may be demonstrated in the Brown Norway rat model of airway inflammation. Male Brown Norway rats

(approx. 200 g) are used for the study of cell accumulation. Food and water are available ad libitum. Ovalbumin (OA) (20 mg/mL) is mixed in a blender (Polytron, Kinematica Ltd.) with aluminium hydroxide (20 mg/mL) and injected (s.c.) concomitantly with B.pertussis vaccine (0.25mL/animal i.p.) on day 1, 15 and 21. On day 28, sensitised animals are restrained in plastic tubes and exposed (1 hour) to an aerosol of OA (3.2mg/mL) using a nose-only exposure system. Animals are killed 48 hours later with pentobarbital (250mg/kg i.p.). The lungs are lavaged using 3 aliquots (4 mL) of Hank's solution (100 mL Hank's balanced salt solution (HBSS) x 10, 100 mL 0.1 M EDTA solution, 10 mL of 1.0 M HEPES solution; 1 L water), the recovered cells pooled and the total volumes of recovered broncho alveolar lavage fluid (BALF) adjusted to 12 mL by addition of Hank's solution.

Compounds under test are administered either locally by intratracheal instillation as a suspension in saline, or orally by gavage in a vehicle comprising (w/v) 43% Cremophor RH40, 34% corn oil glycerides, 10% ethanol, 9% propylene glycol and 4% DMSO, 1 hour prior to and 24 hours after antigen exposure. Control groups of actively sensitized animals receive saline alone with or without exposure to antigen.

In a modification of the above procedure, on day 28 animals are anaesthetised and OA or saline are administered intratracheally, and the animals are killed 24 hours later. In this modified procedure, compounds under test are administered orally by gavage 1 hour prior to and 6 hours after ovalbumin exposure.

Erythrocytes in the BALF are lysed (Quicklyser QLA-200A, TOA Medical Electronics Ltd. Japan). Smears are prepared by diluting the recovered fluid (to approx. 10⁶ cells/mL) and centrifuging an aliquot. The smears are air dried, fixed using a solution of fast green in methanol (2 mg/mL) for 5 seconds and stained with eosin G (5 seconds) and thiazin (5 seconds) in order to differentiate cell types. A total of 500 cells per smear are counted by light microscopy under oil immersion (x 1000). Eosinophil peroxidase activity in the lavage fluid is determined by a method based on the oxidation of o-phenylenediamine (OPD) by eosinophil peroxidase in the presence of hydrogen peroxide (H₂O₂). The BALF (10 µL) is mixed with 100 µL of substrate (1 mM OPD, 1mM H₂O₂, 0.1% Triton-X100, dissolved in 50 mM Tris-HCl pH 8.0) in a 96 well flat bottom microtiter plate and incubated for 30 minutes at room temperature. The reaction is stopped by adding 50 µL H₂SO₄ (4M) and absorbance is measured at 492 nm in a microplate absorbance spectrophotometer. The concentration of eosinophil peroxidase is calculated as units/ml according to the activity of serial dilutions of a standard horseradish peroxidase (Sigma, 210 U/mg dry wt).

Prior administration of compounds of the following Examples reduces eosinophil, neutrophil and total cell count, and reduces eosinophil peroxidase activity compared with untreated controls. For example, the compound of Example 20, administered orally at a dose of 10 mg/kg at -1 hour and +24 hours, shows 70% reduction in eosinophils, 70% reduction in eosinophil peroxidase activity, 70% reduction in neutrophils, and 60% reduction in total cell count, compared with untreated controls; and the compound of Example 1, administered orally at a dose of 10 mg/kg at -1 hour and +6 hours, shows more than 40% reduction in eosinophils and eosinophil peroxidase activity, and about 40% reduction in neutrophils and total cell count, compared with untreated controls.

Having regard to their anti-inflammatory activity, compounds of formula I and their pharmaceutically acceptable salts are indicated for use in the treatment, in particular prophylactic treatment, of obstructive or inflammatory airways disease, e.g. by continued and regular administration over prolonged periods of time, to provide advance protection against recurrence of bronchoconstrictor or other symptomatic attack consequential to obstructive or inflammatory airways disease or to control, ameliorate or reverse basal status of such disease.

The words "treatment" and "treating" as used throughout the present specification and claims in relation to disease, particularly obstructive or inflammatory airways disease, are to be understood accordingly as embracing both prophylactic and symptomatic modes of therapy.

Obstructive or inflammatory airways diseases to which the present invention applies include asthma, pneumoconiosis, chronic obstructive airways or pulmonary disease (COAD or COPD) and adult respiratory distress syndrome (ARDS), as well as exacerbation of airways hyperreactivity consequent to other drug therapy, e.g. aspirin or β -agonist therapy.

The present invention is applicable to the treatment of asthma of whatever type or genesis, including intrinsic and, especially, extrinsic asthma. It is applicable to the treatment of allergic (atopic/IgE-mediated) asthma. It is also applicable to the treatment of non-atopic asthma, including e.g. bronchitic, exercise induced and occupational asthma, asthma induced following bacterial infection and other non-allergic asthmas. It is further applicable to the treatment of wheezy infant syndrome (infant, incipient asthma).

The invention is applicable to the treatment of pneumoconiosis of whatever type or genesis including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tobaccosis and byssionosis.

The invention is applicable to the treatment of COPD or COAD including chronic bronchitis, pulmonary emphysema or dyspnea associated therewith.

The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g. acute, arachidic, catarrhal, chronic, croupus or phthinoic bronchitis.

Having regard to their activity as inhibitors of TNF- α release, compounds of formula I where R is hydrogen and their pharmaceutically acceptable salts are also indicated for use in the down-regulation or inhibition of TNF- α release, e.g. for the treatment of diseases or conditions in which TNF- α release is implicated or plays a mediating role, e.g. diseases or conditions having an aetiology involving or comprising morbid, for example undesirable, excessive or unregulated TNF- α release, in particular for the treatment of cachexia or endotoxin shock and in treatment of AIDS [cf. Sharief et al, Mediators of inflammation, 1 323-338 (1992)].

The invention is applicable to the treatment of cachexia associated with morbid TNF- α release or TNF- α blood-serum levels of whatever origin, including cachexia consequential to, e.g. bacterial, viral or parasitic, infection or to deprivation or deterioration of humoral or other organic, e.g. renal function. It is for example applicable to the treatment of cancerous, malarial and vermal cachexia, cachexia resulting from dysfunction of the pituitary, thyroid or thymus glands as well as uremic cachexia. It is in particular applicable to the treatment of AIDS-related cachexia, i.e. cachexia consequential to or associated with HIV infection.

Having regard to their profile in relation to inhibition of adenosine A3 or A2b receptor activation and inhibition of TNF α release, compounds of formula I and their pharmaceutically acceptable salts are also indicated for use as immunosuppressive agents, e.g. for the treatment of autoimmune diseases, in particular for the treatment of autoimmune diseases in which inflammatory processes are implicated or which have an inflammatory component or aetiology, or as anti-inflammatory agents for the treatment of inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology. Examples of such disease to which the present invention is applicable include

autoimmune haematological disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, allergic rhinitis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), as well as inflammatory and/or hyperproliferative skin diseases such as psoriasis, atopic dermatitis, pemphigus and, in particular, contact dermatitis, e.g. allergic contact dermatitis.

Compounds of formula I and their pharmaceutically acceptable salts are also indicated for use in the treatment of arthritis, and other rheumatic or inflammatory disease, especially for the treatment of rheumatoid arthritis.

Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, compounds of formula I and their pharmaceutically acceptable salts are also indicated for use in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it affects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

Having regard to their ability to interact synergistically with immunosuppressive and/or anti-inflammatory drug substances, compounds of formula I and their pharmaceutically acceptable salts are also indicated for use as co-therapeutic agents for use in conjunction with such drugs, e.g. as potentiators of therapeutic activity of such drugs or as means of reducing required dosaging or potential side effects of such drugs. Such drug substances include, e.g. cyclopeptide, cyclopeptolide or macrolide immunosuppressive or anti-inflammatory drug substances, for example drugs belonging to the cyclosporin class, e.g. cyclosporins A or G,

the drug substances tacrolimus (also known as FK 506), ascomycin and rapamycin and their various known congeners and derivatives, as well as glucocorticosteroid drugs such as budesonide, beclamethasone, fluticasone or mometasone. Diseases to which such co-therapy may be applied include e.g. any disease or condition requiring immunosuppressive or anti-inflammatory drug therapy, e.g. as hereinbefore set forth, in particular for the purposes of immunosuppressive, anti-inflammatory or anti-asthmatic treatment, e.g. to achieve cyclosporin, e.g. cyclosporin A-, macrolide- or steroid-sparing effect.

Accordingly, the present invention further provides a compound of formula I or a pharmaceutically acceptable salt thereof as hereinbefore described for use as a pharmaceutical, for example, where R in formula I is an acyl or monovalent aromatic group, for use in the inhibition of adenosine A3 or A2b receptor activation or, where R in formula I is hydrogen, for use in the inhibition of TNF- α release, and in the treatment of the conditions hereinbefore mentioned, particularly obstructive or inflammatory airways diseases.

In accordance with the foregoing, the present invention also provides a method for the treatment of a condition mediated through release of TNF- α , in particular an obstructive or inflammatory airways disease, which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I where R is hydrogen or a pharmaceutically acceptable salt thereof as hereinbefore described.

In accordance with the foregoing, the present invention further provides a method for the treatment of a condition mediated through activation of the adenosine A3 or A2b receptor which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I or a pharmaceutically acceptable salt thereof as hereinbefore described particularly where R is an acyl group or monovalent aromatic group.

Further in accordance with the foregoing, the invention provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I or a pharmaceutically acceptable salt thereof as hereinbefore described.

Dosages employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of

administration. In general, suitable daily dosages for oral administration are of the order of from 0.2 to 10 mg/kg.

The compounds of formula I or their salts may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; by inhalation, for example in the treatment of asthma; nasally, for example in the treatment of rhinitis; topically to the skin, for example in the treatment of psoriasis; or rectally, for example in the treatment of inflammatory bowel disease.

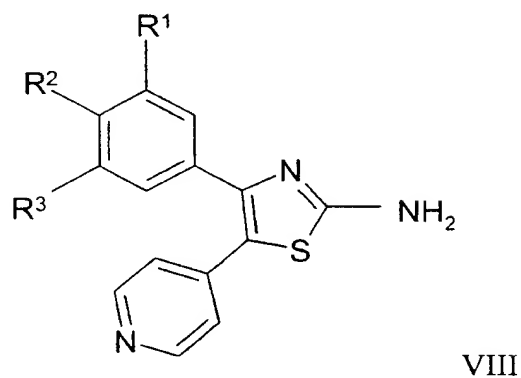
In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

The invention is illustrated by the following Examples, in which in Examples 1 to 19 the compounds of formula I are of formula III as hereinbefore described where R^1 , R^2 , R^3 and R are as shown in the following table

| Example No. | R^1 | R^2 | R^3 | R |
|-------------|-------------------|---|-------------------|--------------------|
| 1 | Cl | Cl | H | CH ₃ CO |
| 2 | H | CH ₃ O | H | CH ₃ CO |
| 3 | H | CH ₃ O | H | pyridin-2-yl |
| 4 | H | CH ₃ O | H | pyridin-3-yl |
| 5 | H | CH ₃ | H | CH ₃ CO |
| 6 | H | CH ₃ | H | pyridin-2-yl |
| 7 | H | CH ₃ | H | pyridin-3-yl |
| 8 | Cl | Cl | H | 4-carboxyphenyl |
| 9 | Br | (CH ₃) ₂ N | H | CH ₃ CO |
| 10 | CH ₃ | H | CH ₃ | CH ₃ CO |
| 11 | CH ₃ | CH ₃ | H | CH ₃ CO |
| 12 | H | CH ₃ (CH ₂) ₃ O | H | CH ₃ CO |
| 13 | CH ₃ O | CH ₃ O | CH ₃ O | CH ₃ CO |

| | | | | |
|----|----|---|---|--------------------------------------|
| 14 | H | benzyloxy | H | CH ₃ CO |
| 15 | H | CH ₃ (CH ₂) ₃ | H | CH ₃ CO |
| 16 | H | (CH ₃) ₂ CH | H | CH ₃ CO |
| 17 | H | CF ₃ | H | CH ₃ CO |
| 18 | H | cyclohexyl | H | CH ₃ CO |
| 19 | Cl | Cl | H | (CH ₃) ₂ CHCO |

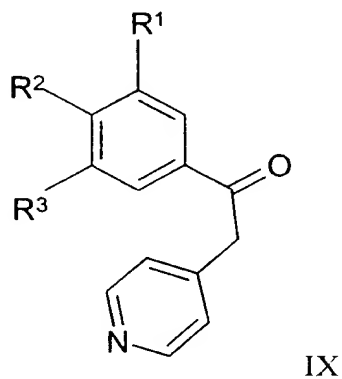
Certain compounds used in the preparation of Examples 1 to 19 are compounds of formula I having the following formula



where R¹, R² and R³ are as shown in the following table

| Example No. | Compound | R ¹ | R ² | R ³ |
|-------------|----------|-------------------|---|-------------------|
| 20 | A | Cl | Cl | H |
| 21 | D | H | CH ₃ O | H |
| 22 | G | H | CH ₃ | H |
| 23 | H | Br | (CH ₃) ₂ N | H |
| 24 | I | CH ₃ | H | CH ₃ |
| 25 | L | CH ₃ | CH ₃ | H |
| 26 | N | H | CH ₃ (CH ₂) ₃ O | H |
| 27 | ZA | CH ₃ O | CH ₃ O | CH ₃ O |
| 28 | ZB | H | benzyloxy | H |
| 29 | ZE | H | CH ₃ (CH ₂) ₃ | H |
| 30 | ZH | H | (CH ₃) ₂ CH | H |
| 31 | ZL | H | CF ₃ | H |
| 32 | ZO | H | cyclohexyl | H |

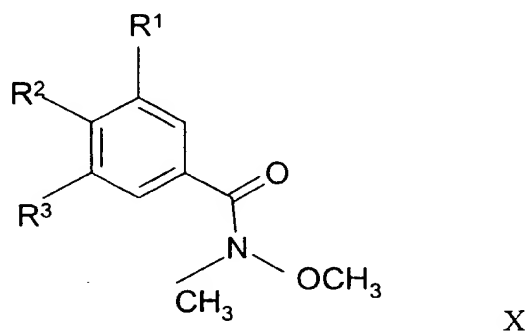
Other compounds used in the preparation of compounds of formula I are of formula



where R^1 , R^2 and R^3 are as shown in the following table

| Compound | R^1 | R^2 | R^3 |
|----------|-----------------|---|-----------------|
| B | Cl | Cl | H |
| E | H | CH ₃ O | H |
| J | CH ₃ | H | CH ₃ |
| M | CH ₃ | CH ₃ | H |
| O | H | CH ₃ (CH ₂) ₃ O | H |
| Q | H | CH ₃ | H |
| R | Br | (CH ₃) ₂ N | H |
| ZC | H | benzyloxy | H |
| ZF | H | CH ₃ (CH ₂) ₃ | H |
| ZI | H | (CH ₃) ₂ CH | H |
| ZM | H | CF ₃ | H |
| ZP | H | cyclohexyl | H |

Other compounds used in the preparation of compounds of formula I are of formula



where R^1 , R^2 and R^3 are as shown in the following table

| Compound | R ¹ | R ² | R ³ |
|----------|-----------------|---|-----------------|
| C | Cl | Cl | H |
| F | H | CH ₃ O | H |
| K | CH ₃ | H | CH ₃ |
| P | H | CH ₃ (CH ₂) ₃ O | H |
| V | CH ₃ | CH ₃ | H |
| ZD | H | benzyloxy | H |
| ZG | H | CH ₃ (CH ₂) ₃ | H |
| ZK | H | (CH ₃) ₂ CH | H |
| ZN | H | CF ₃ | H |
| ZQ | H | cyclohexyl | H |

Compound S is 2-pyridylthiourea, Compound T is 3-pyridylthiourea and Compound U is 4-thioureido-benzoic acid.

The compound of Example 1 is prepared as follows:

Compound A (100mg, 0.31mmol) is dissolved in pyridine (2ml) with stirring under argon and acetyl chloride (30mg, 0.37mmol) is added. A precipitate is formed. The reaction mixture is stirred at room temperature for 2 hours and the solvent is then removed by co-evaporation with toluene three times. The residue is taken up in ethyl acetate and washed with saturated aqueous NaHCO₃ solution. The organic layer is dried over MgSO₄, filtered and evaporated to a yellow solid. This is recrystallized from ethanol/water to give the product as a bright yellow solid, m.p. > 260°C. Microanalysis: Calculated (for 1.95M H₂O) C, 48.61%; H, 3.75%; N, 10.52%; S, 8.02% Found C, 48.67%; H, 3.553%; N, 10.14%; S, 7.695%. MS (CI, NH₃) 363.94.

Compound A (Example 20) is prepared as follows:

Compound B (1.0g, 3.76mmol) is dissolved in dry dioxane (10ml) under argon, and bromine (0.60g, 3.76mmol) is added at room temperature. The mixture is stirred for 5 minutes, after which thin layer chromatography shows complete consumption of starting material. The solvent is removed to give a dark orange gum. This residue is dissolved in absolute ethanol (50ml) with stirring under argon. Thiourea (0.31g, 4.1mmol) is then added and the mixture heated at reflux for 4 hours. The reaction mixture is allowed to cool and the solvent removed. The residue is triturated with ammonia solution, then filtered and washed with water. The solid is taken up in 3M aqueous HCl solution and washed with dichloromethane (DCM), discarding the organic layers. Aqueous ammonia solution is added to the aqueous

layer to pH11 and a precipitate is formed, which is filtered and washed with water. The product is a yellow solid, m.p. 265-266°C. MS (Cl, NH₃) 322.03.

Compound B is prepared as follows:

4-Picoline (0.8g, 8.97mmol) is dissolved in a flame-dried flask under argon in dry tetrahydrofuran (THF) (10ml). The solution is cooled to -20°C and 2.5M BuLi in hexanes (3.6ml, 8.97mmol) is added dropwise. The cooling bath is then removed and the mixture is stirred at room temperature for 1 hour. The resulting red/brown solution is cooled in an ice bath and Compound C (2.1g, 8.97mmol) in THF (6ml) is added dropwise by cannula. The ice bath is removed and the mixture is stirred at room temperature for 18 hours. The solvent is removed by evaporation and the residue taken up in DCM/1.5M HCl. The organic layer is then extracted twice more with 1.5M HCl. The aqueous layer is taken to pH14 (addition of 2M NaOH) and extracted into DCM three times. The organic layer is dried (Na₂SO₄), filtered and concentrated. Purification is achieved through column chromatography, eluting with 33% ethyl acetate/hexane. The product is obtained as a yellow solid, m.p. 87-88°C. MS (Cl, NH₃) 265.92

Compound C is prepared as follows:

3,4-Dichlorobenzoic acid (25g, 130.88mmol) is dissolved in THF (300ml) under argon and N,N'-carbonylbisimidazole (21.2g, 130.88mmol) is added. The mixture is stirred under reflux for 30mins, then cooled and dimethylhydroxylamine hydrochloride (12.7g, 130.88mmol) is added. The mixture is heated under reflux for 6 hours and then left stirring at room temperature overnight. The solvent is removed and the residue taken up in ether 0.25M HCl. The organic layer is washed a further two times with 0.25M HCl and then three times with aqueous 9% Na₂CO₃ and brine. The organic layer is dried (MgSO₄) and concentrated to a colourless oil. The oil is distilled (b.p. 122°C/0.05mmHg) to give the product as a colourless oil. The oil solidifies in the freezer to a white solid, m.p. 60-61°C. MS (Cl, NH₃) 233.94

Compounds D, G, H, I, L, N, ZB, ZE, ZH, ZL and ZO are prepared by procedures analogous to that for Compound A, using Compounds E, Q, R, J, M, O, ZC, ZF, ZI, ZM and ZP respectively in place of Compound B. they have the following characteristics:

| Example | Compound | Melting Point (°C) | MS (Cl, NH ₃) |
|---------|--------------------|--------------------|---------------------------|
| 21 | D (as di-HBr salt) | 200-201 | 283.5 |
| 22 | G | | 268.06 |
| 23 | H | 236-237 | 374.95 |
| 24 | I | 238.5-239.5 | 281.95 |

| | | | |
|----|----|---------------|--------|
| 25 | L | 260-263 (dec) | 281.94 |
| 26 | N | 236-237 | 326.00 |
| 28 | ZB | 228-229 | 359.94 |
| 29 | ZE | 202-203 | 309.97 |
| 30 | ZH | 200-201 | 295.98 |
| 31 | ZL | >270 | 321.88 |
| 32 | ZO | 229-230 | 335.97 |

Compounds E, J, M, O, ZC, ZF, ZI, ZM and ZP are prepared by procedures analogous to that for Compound B, using Compounds F, K, V, P, ZD, ZG, ZK, ZN and ZQ respectively in place of Compound C. They have the following characteristics:

| Compound | Melting Point (°C) | MS (Cl, NH ₃) |
|----------|--------------------|---------------------------|
| E | 102.5-103.5 | 228.03 |
| J | 91.5-92.0 | 226.06 |
| M | 83-84 | 226.06 |
| O | 92-93 | 270.05 |
| ZC | 170-171 | 304.43 |
| ZF | 199-200 | 254.09 |
| ZI | | 240.00 |
| ZM | 96.5-97.5 | 266.00 |
| ZP | 236-237 | 279.98 |

Compounds F, K, P, ZD, ZG, ZK, ZN and ZQ are prepared by procedures analogous to that for Compound C, using the appropriate benzoic acid.

The compounds of Examples 2, 5 and 9 to 19 are prepared by a procedure analogous to that of Example 1 and the compounds of Examples 3, 4 and 6 to 8 are prepared by a procedure analogous to that for Compound A, the reactants and product characteristics being shown in the following table

| Example No. | Melting Point (°C) | MS (Cl, NH ₃) | Reactant Compounds |
|-------------|--------------------|---------------------------|------------------------|
| 2 | 279-280 | 326.03 | D+CH ₃ COCl |
| 3 | 240-241 | 360.40 | E+S |
| 4 | 237-238 | 360.98 | E+T |
| 5 | >270 | 310.05 | G+CH ₃ COCl |

| | | | |
|----|-------------|--------|--|
| 6 | >275 | 345.08 | Q+S |
| 7 | 251-252 | 345.02 | Q+T |
| 8 | >275 | 441.75 | B+U |
| 9 | 275-276 | 418.98 | H+CH ₃ COCl |
| 10 | 272.5-273.5 | 324.08 | I+CH ₃ COCl |
| 11 | 262.5-263.5 | 324.02 | L+CH ₃ COCl |
| 12 | 270-271 | 368.02 | N+CH ₃ COCl |
| 13 | >200 | 386 | ZA+CH ₃ COCl |
| 14 | >270 | 401.94 | ZB+CH ₃ COCl |
| 15 | 252-253 | 352.13 | ZE+CH ₃ COCl |
| 16 | >270 | 338.20 | ZH+CH ₃ COCl |
| 17 | >306 | 364.06 | ZL+CH ₃ COCl |
| 18 | 300-301 | 378.08 | ZO+CH ₃ COCl |
| 19 | 267-268 | 391.95 | A+(CH ₃) ₂ CHCOCl |

The compounds of Examples 33 to 49 are compounds of formula III as hereinbefore described where R³ is hydrogen and R¹, R² and R are as shown in the following table:

| Example | R ¹ | R ² | R |
|---------|-----------------|-----------------------|--------------------|
| 33A | CF ₃ | H | CH ₃ CO |
| 33B | CF ₃ | H | H |
| 34A | F | CF ₃ | CH ₃ CO |
| 34B | F | CF ₃ | H |
| 35A | CH ₃ | H | CH ₃ CO |
| 35B | CH ₃ | H | H |
| 36A | Cl | H | CH ₃ CO |
| 36B | Cl | H | H |
| 37A | H | 3,4-dichlorobenzyloxy | CH ₃ CO |
| 37B | H | 3,4-dichlorobenzyloxy | H |
| 38A | H | 2-phenylethoxy | CH ₃ CO |
| 38B | H | 2-phenylethoxy | H |
| 39A | H | Br | CH ₃ CO |
| 39B | H | Br | H |
| 40A | H | 4-methylbenzyloxy | CH ₃ CO |
| 40B | H | 4-methylbenzyloxy | H |
| 41A | H | 4-chlorobenzyloxy | CH ₃ CO |

| | | | |
|-----|-------------------|-------------------|------------------------------------|
| 41B | H | 4-chlorobenzyloxy | H |
| 42A | CH ₃ | benzyloxy | CH ₃ CO |
| 42B | CH ₃ | benzyloxy | H |
| 43A | Cl | benzyloxy | CH ₃ CO |
| 44A | H | benzyloxy | pyridin-2-yl |
| 45A | H | benzyloxy | pyridin-3-yl |
| 46A | CH ₃ O | benzyloxy | CH ₃ CO |
| 46B | CH ₃ O | benzyloxy | H |
| 47A | CH ₃ O | benzyloxy | CH ₃ CH ₂ CO |
| 47B | CH ₃ O | benzyloxy | H |
| 48A | H | benzyloxy | 3-furoyl |
| 48B | H | benzyloxy | H |
| 49A | H | H | CH ₃ CO |
| 49B | H | H | H |

The compounds of Examples 33A to 43A and 46A to 49A are prepared from Examples 33B to 43B and 46B to 49B respectively by a procedure analogous to that of Example 1. The compounds of Examples 44A and 45A are prepared respectively from Examples 44C and 44C hereinafter described by a procedure analogous to that used for the preparation of Compound A. The compounds of Examples 33B to 43B and 46B to 49B are prepared respectively from Examples 33C to 43C and 46C to 49C hereinafter described by a procedure analogous to that used for preparation of Compound A. The compound designated as Example 47B is identical to that designated as Example 46B. The compounds have the following characteristics:

| Example | Melting Point (°C) | MS(Cl,NH ₃) |
|---------|--------------------|-------------------------|
| 33A | >300 | 363 |
| 33B | 222-223 | 320 |
| 34A | >270 | 339 |
| 34B | >270 | 338 |
| 35A | >265 | 308 |
| 35B | >245 | 266 |
| 36A | >265 | 329 |
| 36B | >245 | 287 |
| 37A | >275 | 469 |
| 37B | 196-199 | 427 |
| 38A | 263-264 | 415 |

| | | |
|-----|----------------|-----|
| 38B | 164-165 | 373 |
| 39A | >300 | 373 |
| 39B | >275 | 331 |
| 40A | 263-264 | 414 |
| 40B | 217-220 | 372 |
| 41A | >275 | 435 |
| 41B | 227-229 | 393 |
| 42A | 249-251 | 414 |
| 42B | 95-98 | 372 |
| 43A | 238-240 | 435 |
| 43B | 120-124 | 393 |
| 44A | 250-252 | 435 |
| 45A | 133-138 | 435 |
| 46A | 216-218 | 430 |
| 46B | 110-113 | 388 |
| 47A | 220-222 | 444 |
| 47B | 110-113 | 388 |
| 48A | 232-234 | 454 |
| 48B | 228-229 | 359 |
| 49A | >275 | |
| 49B | known compound | |

Examples 33C to 49C are compounds of formula IX as hereinbefore described where R³ is hydrogen and R¹ and R² are as shown for Examples 33A to 49A respectively in the above table. They are prepared from Examples 33D to 49D respectively hereinafter described by a procedure analogous to that used for the preparation of Compound B. Examples 33D to 49D are compounds of formula X as hereinbefore described where R³ is hydrogen and R¹ and R² are as shown for Examples 33A to 49A respectively in the above table. They are prepared from the corresponding benzoic acid by a procedure analogous to that used for the preparation of compound C. The compounds designated as Examples 44C, 45C and 48C are identical, as are those designated as Examples 44D, 46D and 48D. The compounds have the following characteristics:

| Example | Melting Point (°C) | MS(Cl,NH ₃) |
|---------|--------------------|-------------------------|
| 33C | 74-75 | 264 |
| 33D | OIL | 232 |
| 34C | 73-74 | 282 |

| | | |
|-----|----------------|-----|
| 34D | OIL | 250 |
| 35C | 116-117 | 210 |
| 35D | OIL | 178 |
| 36C | 104-105 | 231 |
| 36D | OIL | 199 |
| 37C | 164-167 | 371 |
| 37D | OIL | 340 |
| 38C | 85-86 | 316 |
| 38D | OIL | 284 |
| 39C | 128-129 | 275 |
| 39D | OIL | 243 |
| 40C | 164-166 | 316 |
| 40D | 98-100 | 284 |
| 41C | 125-127 | 336 |
| 41D | 78-80 | 304 |
| 42C | 116-118 | 316 |
| 42D | 74-76 | 284 |
| 43C | 124-125 | 336 |
| 43D | 86-88 | 304 |
| 44C | 170-171 | 303 |
| 44D | 60-61 | 271 |
| 45C | 170-171 | 303 |
| 45D | 60-61 | 271 |
| 46C | 78-80 | 332 |
| 46D | 89-91 | 300 |
| 47C | 78-80 | 333 |
| 47D | 89-91 | 301 |
| 48C | 170-171 | 303 |
| 48D | 60-61 | 271 |
| 49C | known compound | |
| 49D | known compound | |

Example 50

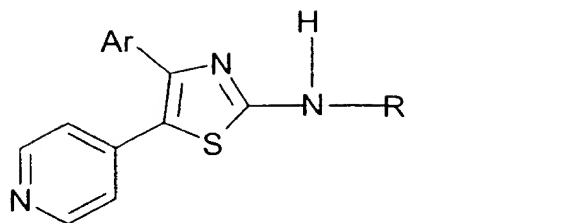
Example 50A is a compound of formula IIIa as hereinbefore described where R is acetyl; it is prepared from Example 50B by a procedure analogous to that of Example 1. Example 50B is a compound of formula IIIa where R is hydrogen; it is prepared from Example 50C by

a procedure analogous to that used for the preparation of Compound A. Example 50C is a compound of formula IV where Ar is a group of formula IIa in which R¹ is hydrogen, R² is chlorine and R³_a is methyl; it is prepared from Example 50D by a procedure analogous to that used for the preparation of Compound B. Example 50D is a compound of formula VII where Ar is as for Example 50C; it is prepared from the corresponding benzoic acid by a procedure analogous to that used for the preparation of Compound C. The compounds have the following characteristics:

| Example | Melting Point (°C) | MS(Cl,NH ₃) |
|---------|--------------------|-------------------------|
| 50A | >275 | 343 |
| 50B | >270 | 301 |
| 50C | 70-71 | 244 |
| 50D | OIL | 213 |

Claims

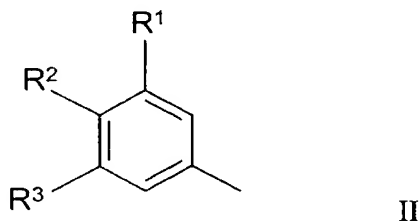
1. A compound which is of formula



or is a salt of a compound of formula I, where Ar is an unsubstituted or substituted aryl group linked through an aromatic ring carbon atom thereof to the indicated thiazole ring and R is hydrogen, an acyl group or a monovalent aromatic group having up to 10 carbon atoms linked through an aromatic ring carbon atom to the indicated nitrogen atom, provided that R is not hydrogen when Ar is phenyl or 4-methoxyphenyl.

2. A compound according to claim 1, in which Ar is phenyl which is unsubstituted or substituted by one or more substituents selected from halogen, unsubstituted or halogen-substituted C₁ to C₈ alkyl, C₁ to C₈ alkoxy, C₇ to C₁₁ aralkyloxy, C₅ to C₈ cycloalkyl, C₁ to C₈ alkylamino or di (C₁-C₈ alkyl)amino.

3. A compound according to claim 1, in which Ar is a group of formula



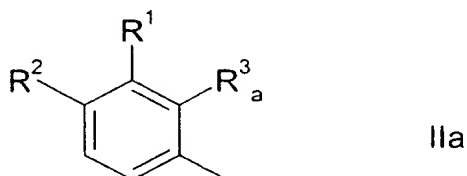
where R¹, R² and R³ are each independently hydrogen, halogen, unsubstituted or halogen-substituted C₁ to C₄ alkyl, C₁ to C₄ alkoxy, C₇ to C₉ aralkyloxy, C₆ to C₇ cycloalkyl, C₁ to C₄ alkylamino or di(C₁-C₄alkyl)amino.

4. A compound according to claim 3, in which one or two of R¹, R² and R³ are hydrogen.

5. A compound according to claim 3 or 4, in which R¹ is hydrogen, chlorine, bromine, methoxy or methyl, R² is hydrogen, chlorine, methyl, trifluoromethyl, isopropyl, n-butyl, cyclohexyl, methoxy, n-butoxy, benzyloxy or N-dimethylamino and R³ is hydrogen, methoxy or methyl.

6. A compound according to claim 3 or 4, in which R^1 is hydrogen or trifluoromethyl, R^2 is hydrogen, 3,4-dichlorobenzoyloxy, 2-phenylethoxy, bromine, 4-methylbenzyloxy, or 4-chlorobenzoyloxy, and R^3 is hydrogen.

7. A compound according to claim 1, in which Ar is a group of formula



where R^1 and R^2 are as defined in claim 3 and R^3_a is C_1 to C_4 alkyl.

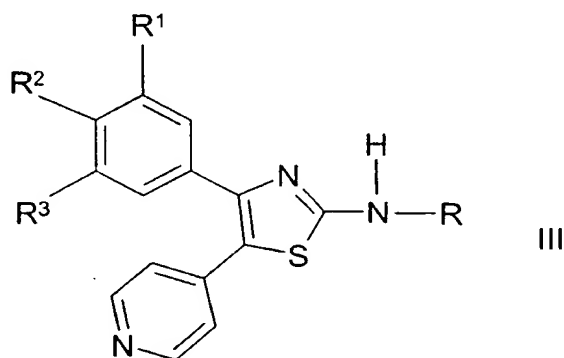
8. A compound according to any one of the preceding claims in which R is an acyl group of formula R^4CO- where R^4 is a C_1 to C_4 alkyl group, or R is a phenyl group which is unsubstituted or substituted by carboxy, or R is a 6-membered nitrogen heteroaryl group.

9. A compound according to any one of claims 1 to 7, in which R is an acyl group of formula R^4_aCO- where R^4_a is a 5-membered heteroaryl group.

10. A compound according to claim 8, in which R is acetyl, isobutyryl, carboxyphenyl or pyridinyl.

11. A compound according to claim 8, in which R is propionyl or 3-furoyl.

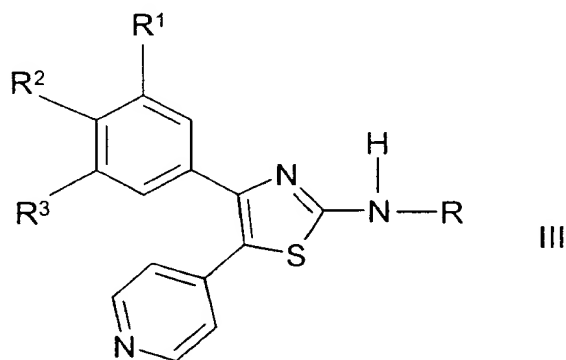
12. A compound according to claim 1 which is a compound of formula



or a pharmaceutically acceptable salt thereof where

- (i) R^1 and R^2 are chlorine, R^3 is hydrogen and R is hydrogen, acetyl, isobutyryl, or 4-carboxyphenyl; or
- (ii) R^1 and R^3 are hydrogen, R^2 is methoxy or methyl and R is hydrogen, acetyl, pyridin-2-yl or pyridin-3-yl; or
- (iii) R^1 is bromine, R^2 is N-dimethylamino, R^3 is hydrogen and R is hydrogen or acetyl; or
- (iv) R^1 and R^3 are methyl, R^2 is hydrogen and R is hydrogen or acetyl; or
- (v) R^1 is methyl, R^2 is methyl, R^3 is hydrogen and R is hydrogen or acetyl; or
- (vi) R^1 and R^3 are hydrogen, R^2 is n-butoxy, benzyloxy, n-butyl, isopropyl, trifluoromethyl or cyclohexyl and R is hydrogen or acetyl; or
- (vii) R^1 , R^2 and R^3 are methoxy and R is hydrogen or acetyl.

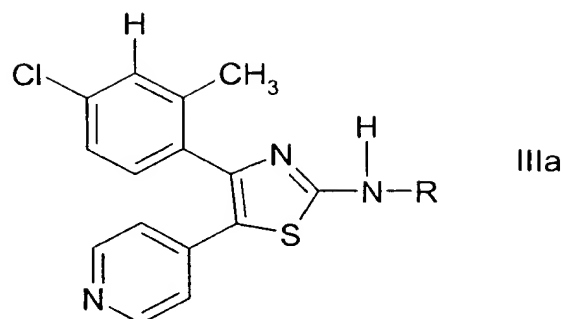
13. A compound according to claim 1 which is a compound of formula



or a pharmaceutically acceptable salt thereof where

- (viii) R^1 is methyl, chlorine or trifluoromethyl, R^2 and R^3 are hydrogen and R is hydrogen or acetyl;
- (ix) R^1 is fluorine, R^2 is trifluoromethyl, R^3 is hydrogen and R is hydrogen or acetyl;
- (x) R^1 is hydrogen, R^2 is chlorine, R^3 is methyl and R is hydrogen or acetyl;
- (xi) R^1 and R^3 are hydrogen, R^2 is 3,4-dichlorobenzyloxy, 2-phenylethoxy, bromine, 4-methylbenzyloxy or 4-chlorobenzyloxy and R is hydrogen or acetyl;
- (xii) R^1 is methyl, chlorine or methoxy, R^2 is benzyloxy, R^3 is hydrogen and R is hydrogen or acetyl;
- (xiii) R^1 and R^3 are hydrogen, R^2 is benzyloxy, and R is 2-pyridinyl, 3-pyridinyl or 3-furoyl;
- (xiv) R^1 is methoxy, R^2 is benzyloxy, R^3 is hydrogen and R is propionyl; or
- (xv) R^1 , R^2 and R^3 are each hydrogen.

14. A compound according to claim 1 which is a compound of formula



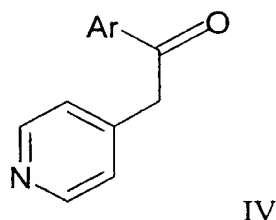
where R is hydrogen or acetyl, or a pharmaceutically acceptable salt thereof.

15. A compound according to any one of claims 1 to 14 for use as a pharmaceutical.
16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14 together with a pharmaceutically acceptable diluent or carrier therefor.
17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14 for use in the treatment of a disease mediated through activation of the adenosine A3 or adenosine A2b receptor or, where R is hydrogen, for use in treatment of a disease mediated through release of TNF- α .
18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14 for use in treatment of an obstructive or inflammatory airways disease.
19. Use of a compound according to any one of claims 1 to 14 in the preparation of a medicament for the treatment of a disease mediated through activation of the adenosine A3 or adenosine A2b receptor or, where R is hydrogen, for the treatment of a disease mediated through release of TNF- α .
20. Use of a compound according to any one of claims 1 to 14 in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.
21. A method for a treatment of a disease mediated through activation of the adenosine A3 or adenosine A2b receptor which comprises administering to a subject in need thereof a compound according to any one of claims 1 to 14.

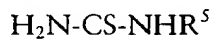
22. A method for the treatment of a condition mediated through release of TNF- α which comprises administering to a subject in need thereof a compound according to any one of claims 1 to 14 where R is a hydrogen atom.

23. A method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject in need thereof a compound according to any one of claims 1 to 14.

24. A method of preparing a compound of formula I according to claim 1 which comprises reacting a compound of formula

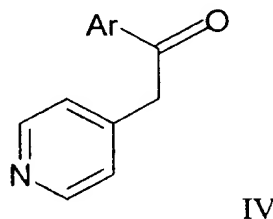


with halogen and then reacting the halogenated product with a compound of formula



where Ar is as defined in claim 1 and R^5 is hydrogen or a monovalent aromatic group having up to 10 carbon atoms linked through an aromatic ring carbon atom to the indicated nitrogen atom and, where R^5 is hydrogen and a compound of formula I in which R is acyl is desired, reacting the compound obtained with an acylating agent.

25. A compound of formula



where Ar is as defined in any one of claims 1 to 7, provided that Ar is not 4-methoxyphenyl, 4-methylphenyl, 3-bromo-4-dimethylaminophenyl, 4-benzyloxyphenyl or 4-trifluoromethylphenyl.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03859

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D417/04 C07D417/14 C07D213/50 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|---------------------------------|
| A | EP 0 149 884 A (TAKEDA) 31 July 1985 (1985-07-31) claims; table 1 --- | 1-4, 12, 13, 16-20 |
| X | EP 0 308 020 A (MERCK) 22 March 1989 (1989-03-22) page 13 -page 16; example 11 --- | 25 |
| X | WO 96 18626 A (HOFFMAN LA ROCHE) 20 June 1996 (1996-06-20) page 19 -page 20; example II --- | 25 |
| P, X | WO 99 21555 A (TAKEDA) 6 May 1999 (1999-05-06) page 61 -page 76; claims; tables 2, 5-7, 10-21 ----- | 1-3, 5, 12, 13, 15-20, 25 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

14 September 1999

Date of mailing of the international search report

23/09/1999

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 03859

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21-23
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 21-23
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/03859

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 149884 A | 31-07-1985 | JP 1796705 C | 28-10-1993 |
| | | JP 5003468 B | 14-01-1993 |
| | | JP 61010580 A | 18-01-1986 |
| | | JP 60058981 A | 05-04-1985 |
| | | AT 83483 T | 15-01-1993 |
| | | AU 567754 B | 03-12-1987 |
| | | AU 3243384 A | 14-03-1985 |
| | | CA 1255663 A | 13-06-1989 |
| | | DE 3486009 A | 28-01-1993 |
| | | US 4612321 A | 16-09-1986 |
| EP 308020 A | 22-03-1989 | JP 1128969 A | 22-05-1989 |
| WO 9618626 A | 20-06-1996 | AU 4301096 A | 03-07-1996 |
| | | BR 9509998 A | 30-12-1997 |
| | | CA 2207404 A | 20-06-1996 |
| | | CN 1175252 A | 04-03-1998 |
| | | EP 0797575 A | 01-10-1997 |
| | | FI 972492 A | 12-06-1997 |
| | | JP 10510281 T | 06-10-1998 |
| | | TR 960543 A | 21-07-1996 |
| WO 9921555 A | 06-05-1999 | AU 9648098 A | 17-05-1999 |